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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,374	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21 and 49-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15-19 and 49-53* is/are rejected.

7)☒ Claim(s) *13,14,21,52 and 54-66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office communication filed on May 27, 2004 has been entered. Since this office communication and the office action filed on February 24, 2004 consist of a complete response to the office action mailed on October 20, 2003, both the office communication filed on May 27, 2004 and the response to the office action filed on February 24, 2004 have been entered. The claims pending in this application are claims 1-19, 21, and 49-66. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on February 24, 2004.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 2, 4, 5, 10, 19, 49-51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Brow *et al.*, (US Patent No. 6,001,567, published on December 14, 1999).

The invention is directed to an intact charge-switch nucleotide phosphate (NP). Claim 1 requires that an intact NP probe has a terminal phosphate with a fluoroscope moiety attached thereto and said intact NP probe has a first molecular charge associated therewith,

whereupon cleavage of said terminal phosphate as a phosphate fluorophore moiety, said phosphate fluoroscope moiety carries a second molecular charge, wherein the difference between said first molecular charge and said second molecular charge is at least 0.5. Claim 2 further limits claim 1 and requires that either said intact NP probe has a positive molecular charge, or wherein upon cleavage of said terminal phosphate fluorophore moiety, said terminal phosphate fluorophore moiety carries a molecular positive charge relative to said intact NP probe. Claim 4 requires that said intact charge-switch NP probe has a positive charge. Claim 5 requires that, upon cleavage of said terminal phosphate as a pyrophosphate fluorophore moiety, said pyrophosphate fluorophore moiety carries a positive charge relative to said intact charge-switch NP probe. Claim 10 further limits claim 10 and requires that said fluorophore moiety is a member selected from the group consisting of fluorescein, 5-carboxyfluorescein (FAM), rhodamine, 5-(2'-aminoethyl) aminonapthalene-1-sulfonic acid (EDANS), anthranilamide, coumarin, terbium chelate derivatives, Reactive Red 4, BODIPY dyes and cyanine dyes. Claim 19 further limits claim 1 and requires that the difference between said first molecular charge and said second molecular charge is from 0.5 to 4.0. Claim 49 requires, that upon enzymatic cleavage of an intact charge-switch NP probe to produce a phosphate detectable moiety, said phosphate detectable moiety migrates to an electrode, and said intact charge-switch NP probe migrates to the other electrode. "charge-switch nucleotide" is defined as "a labeled nucleotide phosphate (e.g., γ-NP-Dye) that upon release or cleavage of a phosphate detectable moiety (e.g., PPi-Dye) has a different net charge associated with the cleavage product compared to the intact nucleotide phosphate probe (e.g., γ- NP-Dye). In certain preferred aspects, the attachment of the dye to the PPi is via a nitrogen in lieu of an oxygen. Preferably, the charge difference between the intact

γ-NP-Dye and the PPi-Dye is at least 0.5, and more preferably about 1 to about 4" (see the specification, page 7, last paragraph bridging to page 8, first paragraph). "phosphate detectable moiety" is defined as "a detectable cleavage product from a NP probe of the present invention. Examples include, but are not limited to, PPi-Dye, PP-F, P-Dye, a phosphate fluoroscope moiety, a terminal phosphate fluoroscope moiety, a detectable moiety, charged groups, electrically active groups, detectable groups, reporter groups, combinations thereof, and the like." (see the specification, page 8, third paragraph). Claim 50 further limits claim 49 and requires that said intact NP probe either has a positive molecular charge or, upon cleavage of said phosphate detectable moiety, said phosphate detectable moiety carries a different charge relative to said intact NP probe. Claim 51 further limits claim 49 and requires that said intact NP probe either has a negative molecular charge or, upon cleavage of said phosphate detectable moiety, said phosphate detectable moiety carries a different charge relative to said intact NP probe. Claim 53 further limits claim 49 and requires that said intact NTP probe has a positive charge.

Brow *et al.*, teach detection of nucleic acid sequences by invader-directed cleavage. A modified oligonucleotide 61 (5'-Cy3-AminoT-Amino-TCTTTTCACCAGCGAGAC GGG-3') carried a net negative charge. After cleavage with a cleavage enzyme, the following oligonucleotides were generated: 5'-CTTTTCACCAGCGAGACGGG-3' (residues 3-22 of SEQ ID NO:61) and 5'-Cy3-AminoT-Amino-T-3'. 5'-Cy3-AminoT-Amino-T-3' bore a detectable moiety (the positively-charged Cy3 dye) and two amino-modified bases. Since, in the 5'-Cy3-AminoT-Amino-T-3'oligonucleotide, the amino-modified bases and the Cy3 dye contributed positive charges in excess of the negative charges contributed by the phosphate groups, this oligonucleotide had a net positive charge. The other, longer cleavage fragment bore

a net negative charge (see lines 39-65 in column 22, lines 50-67 in column 97, and lines 1-28 in column 98). As shown in Figure 56 and Example 23, compounds 70 or 74 contained two amino modified thymidines that, under reaction conditions, displayed positively charged R-NH_3^+ groups attached at the C5 position through a C_{10} or C_6 linker, respectively. The compound 70 or 74 possessed a Cy-3 dye positioned at the 5'-end which individually was positively charged under reaction and isolation conditions described in this example. Because compounds 70 or 74 were 3'-end phosphorylated, they consisted of four negative charges and three positive charges. For the simplicity of analysis, each group was assigned a whole number of charges, although it was realized that, depending on the pKa of each chemical group and ambient pH, a real charge might differ from the whole number assigned. This difference was not significant over the range of pHs used in the enzymatic reactions studied here (see Figure 56 and lines 12-41 of column 96).

Regarding claims 49-51, charge-switch nucleotide is defined as a labeled nucleotide phosphate (e.g., γ-NP-Dye) that upon release or cleavage of a phosphate detectable moiety (e.g., PPi-Dye) has a different net charge associated with the cleavage product compared to the intact nucleotide phosphate probe (e.g., γ- NP-Dye) wherein a labeled nucleotide phosphate, a phosphate detectable moiety, and the intact nucleotide phosphate probe are not limited to γ-NP-Dye, Ppi-Dye, and γ- NP-Dye respectively while phosphate detectable moiety is defined as a detectable cleavage product from a NP probe but are not limited to, PPi-Dye, PP-F, P-Dye, a phosphate fluoroscope moiety, a terminal phosphate fluoroscope moiety, a detectable moiety, charged groups, electrically active groups, detectable groups, reporter groups, and combinations thereof. Since it is generally accepted that oligonucleotide is a probe, modified oligonucleotide

61 is a probe. Since the modified oligonucleotide 61 bears a net negative charge and the modified oligonucleotide 61, upon enzymatic cleavage (ie., a cleavage enzyme), releases a shorter cleavage fragment 5'-Cy3-AminoT-Amino-T-3' having a net positive charge, the modified oligonucleotide 61 is a NP probe and 5'-Cy3-AminoT-Amino-T-3' is a phosphate detectable moiety since it carries the phosphate groups and a fluorescence dye (ie., Cy3) wherein said phosphate detectable moiety (ie., 5'-Cy3-AminoT-Amino-T-3') carries a different charge relative to said intact NP probe (ie., the modified oligonucleotide 61) as recited in claims 50 and 51. Since it is known that an oligonucleotide having a net positive charge migrates toward the negative electrode in an electrical field while an oligonucleotide having a net negative charge migrates toward the positive electrode in an electrical field (see lines 6-21 in column 23), the NP probe (ie., modified oligonucleotide 61) migrates toward the positive electrode in an electrical field while the phosphate detectable moiety (ie., 5'-Cy3-AminoT-Amino-T-3') migrates toward the negative electrode in an electrical field as recited in claim 49. Although claims 50 and 53 require that said intact NP probe has a positive charge while Brow *et al.*, disclose that intact NP probe (ie., the modified oligonucleotide 61) has positive charges, since "has" of claims 49 and 53 is considered as "comprising", claims 50 and 53 do not limit that said intact NP probe has only one positive charge, claims 50 and 52 are anticipated by Brow *et al.*.

Regarding claims 1, 2, 4, 5, 10, and 19, since the Cy-3 dye of the compound 70 or 74 is attached to a phosphate group positioned at the 5'-end of the compound (see Figure 58), the phosphate group positioned at the 5'-end of the compound is a terminal phosphate with a fluorophore moiety attached thereto as recited in claim 1. Since, if the compound 76 is cleaved on a 3', 5'-phosphodiester bond which is related to the first phosphate (for the location of cleaved

3', 5'-phosphodiester bond, see arrow in attached Figure 58 in previous office action), the phosphate group positioned at the 5'-end of the compound (ie., a terminal phosphate with a fluorophore moiety attached thereto) is released from the compound 76 and the released compound is a phosphate fluorophore moiety as recited in claim 1 since the released compound has a fluorophore moiety. Since the released compound consists of two negative charge and a positive charges and has net charge -1 (see attached Figure 58) while the compound 76 consists of four negative charges and two positive charges and has net charge -2, the compound 76 and the released compound are an intact NP probe and a phosphate fluorophore moiety respectively wherein the difference between said first molecular charge (ie., -2) and said second molecular charge(ie., -1) is at least 0.5 [ie., 1] as recited in claims 1 and 19 and said intact charge-switch NP probe has a positive charge as recited in claim 4, and, upon cleavage of said terminal phosphate as a pyrophosphate fluorophore moiety (ie., the released compound), said pyrophosphate fluorophore moiety carries a positive charge (ie., -1) relative to said intact charge-switch NP probe (ie., -2) as recited in claim 5. Since the compound 76 consists of four negative charges and two positive charges, said intact NP probe (ie., the compound 76) has a positive molecular charge as recited in claim 2. Since it is known that cy3 is one of cyanine dyes, claim 10 is anticipated by Brow *et al.*.

Therefore, Brow *et al.*, teach all limitations recited in claims 1, 2, 4, 5, 10, 19, 49-51 and 53.

Response to Arguments

In page 9, third paragraph bridging to page 14, third paragraph of applicant's remarks filed on February 24, 2004, applicant argues that: (1) "the present invention provides a 'charge-

switch nucleotide phosphate (NP) probe' . The NP probe is a single monomer, having a single base, a single sugar and a least one phosphate group" since "[T]he terms 'a charge-switch nucleotide phosphate (NP) probe', 'a NP probe' and 'a charge-switch nucleotide' are used interchangeably and are defined on page 7, bridging to the top of page 8" of the specification; and (2) "[B]row et al. teaches an oligonucleotide as a molecule comprised of two or more deoxyribonucleotides or ribonucleotides. The oligonucleotides of Brow et al. are structurally different and are used for an entirely different purpose than, the charge-switch nucleotides of the present invention".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. In view of the specification, the examiner does not find in the specification that "[T]he terms 'a charge-switch nucleotide phosphate (NP) probe', 'a NP probe' and 'a charge-switch nucleotide' are used interchangeably" as suggested by applicant. Since the specification only defines "a charge-switch nucleotide" (see page 7, bridging to the top of page 8 of the specification) and has no definitions for "charge-switch nucleotide phosphate (NP) probe" and "NP probe", the NP probe is not limited to a single monomer having a single base, a single sugar and a least one phosphate group as suggested by applicant and it is reasonably to consider the modified oligonucleotide 61 taught by Brow *et al.*, as a NP probe. Furthermore, the claims are drawn to a NP probe "comprising" . The open language "comprising" encompasses any additional elements (ie., nucleotides) taught in the prior art. Hence, even if applicant asserted that definition of NP probe was found convincing, the claims, as written, encompass the oligonucleotide taught by Brow *et al.*.

4. Claims 1-4, 6-12, and 15-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Williams *et al.*, (US Patent No. 6,232,075 B1, filed on December 13, 1999, priority date: December 14, 1998).

The invention is directed to an intact charge-switch nucleotide phosphate (NP) probe. Claim 1 requires that an intact NP probe has a terminal phosphate with a fluoroscope moiety attached thereto and said intact NP probe has a first molecular charge associated therewith, whereupon cleavage of said terminal phosphate as a phosphate fluorophore moiety, said phosphate fluoroscope moiety carries a second molecular charge, wherein the difference between said first molecular charge and said second molecular charge is at least 0.5. Claim 2 further limits claim 1 and requires that either said intact NP probe has a positive molecular charge, or wherein upon cleavage of said terminal phosphate fluorophore moiety, said terminal phosphate fluorophore moiety carries a molecular positive charge relative to said intact NP probe. Claim 3 further limits claim 1 and requires that said terminal phosphate is a pyrophosphate with a fluorophore moiety attached thereto. Claim 4 requires that said intact charge-switch NP probe has a positive charge. Claim 6 requires that said intact charge-switch NP probe is dNTP or NTP. Claim 7 further limits claim 6 and requires that said intact charge-switch NP probe is dNTP. Claim 8 further limits claim 7 and requires that dNTP is a member selected from the group consisting of deoxyadenosine triphosphate, deoxycytosine triphosphate, deoxyguanosine triphosphate, deoxythymidine triphosphate and deoxyuridine triphosphate. Claim 9 further limits claim 6 and requires that NTP is a member selected from the group consisting of adenosine triphosphate, cytosine triphosphate, guanosine triphosphate and uridine triphosphate. Claim 10 further limits claim 10 and requires that said fluorophore moiety is a member selected from the

group consisting of fluorescein, 5-carboxyfluorescein (FAM), rhodamine, 5-(2'-aminoethyl) aminonapthalene-l-sulfonic acid (EDANS), anthranilamide, coumarin, terbium chelate derivatives, Reactive Red 4, BODIPY dyes and cyanine dyes. Claim 11 further limits claim 3 and requires that said fluorophore moiety is attached to said terminal phosphate via a linker. Claim 12 further limits claim 11 and requires that said fluorophore linker is an alkylene group having between about 5 to about 12 carbons. Claim 15 further limits claim 1 and requires that at least one of the phosphate moieties of said nucleotide phosphate probe has an ionized oxygen atom with a counter-cation associated therewith. Claim 16 further limit the counter-cation recited in claim 15 and requires that said counter-cation is a metal ion. Claim 17 further limits the metal ion recited in claim 16 and requires that said metal ion is selected from the group consisting of Mg^{++}, Mn^{++}, K^{+} and Na^{+}. Claim 18 further limits claim 11 and requires that wherein said fluorophore moiety is BODIPY TR. Claim 19 further limits claim 1 and requires that the difference between said first molecular charge and said second molecular charge is from 0.5 to 4.0.

Williams *et al.*, teach heterogeneous assay for pyrophosphate detection. Figure 4 showed a nucleotide triphosphate (NTP) probe comprising a dNTP having a γ phosphate with a fluorophore moiety attached thereto and a quencher moiety sufficiently proximal to the fluorophore moiety to prevent fluorescence of the fluorophore moiety (see Figure 4, and columns 3 and 4). As illustrated in Figure 1A, dNTP incorporation into a growing oligonucleotide by a DNA polymerase such as T7 DNA polymerase resulted in pyrophosphate cleavage. In this reaction, the phosphate ester bond between the α and β phosphates of the incorporated nucleotide was cleaved by the DNA polymerase, and the β-γ-diphosphate (pyrophosphate) was released in

solution. In the situation wherein a fluorophore was attached to the γ phosphate of the dNTP, the fluorophore was released from the nucleotide along with the pyrophosphate group (see Figures 1A, 1B, and 2C, and lines 23-63 of column 6).

Regarding claims 1, 15-17, and 19, since the γ phosphate of the dNTP in Figure 4 is attached to a fluorophore, the dNTP taught by Williams *et al.*, is a NP probe having a terminal phosphate with a fluoroscope moiety as recited in claim 1. As taught by Williams *et al.*, dNTP incorporation into a growing oligonucleotide by a DNA polymerase results in pyrophosphate cleavage. Since in example 3, DABCYL-dUTP or DABCYL-dUTP-thiol or DABCYL-dUTP-BODIPY TR is stored in a buffer at pH 7 (ie.,Buffers A and B) after they are purified from a reversed-phase HPLC (see column 18, lines 61-67 and column 19, lines 1-29) and one of DNA polymerases used by Williams *et al.*, is T7 DNA polymerase (see column 6, lines 23-36 and column 18, lines 1-9), and it is known that pH for reaction buffer of T7 DNA polymerase is 7.5 (see the attachment for T7 DNA polymerase), dNTP taught by Williams *et al.*, is in either a buffer with a pH 7 or a buffer with pH 7.5. Since various different fluorescence dyes such as cy3 or cy5 are used as the fluorophore moiety and the quencher moiety in fluorescence labeled dNTP (see columns 12 and 13), **in one of dNTPs of Figure 4, its fluorophore moiety does not bear any charge and its quencher moiety is cy3**. Since it is known that cy3 is a fluorescence dye carrying a net single positive charge (see page 2, last paragraph of the attachment for CyDye in previous office action) and dNTP in Figure 4 of Williams *et al.*, has three negative charges (see Figure 4) while the bases in dNTP are mostly uncharged at pH from about 6.5 to about 8.5 (see the specification, page 11, third paragraph), under an ideal condition (without considering effects of a buffer), net charge of the dNTP in

Figure 4 of Williams *et al.*, is -2. Since the fluorophore moiety can be released from the dNTP along with the pyrophosphate group after the cleavage (see Figure 2) and the fluorophore moiety do not bear any charge, under an ideal condition (without considering effects of a buffer), net charge of pyrophosphate (PPi)-the fluorophore moiety released from the dNTP in Figure 4 of Williams *et al.*, is -3 (with three negative charges, for PPi structure, see Figure 1 of the specification). Therefore, under an ideal condition (without considering effects of a buffer), dNTP in Figure 4 of Williams *et al.*, which has a γ phosphate with a fluorophore moiety that does not bear any charge and has cy3 quencher moiety, is an intact NP probe having a terminal phosphate with a fluoroscope moiety attached thereto, said intact NP probe having a first molecular charge associated therewith (ie., -2), whereupon cleavage of said terminal phosphate as a phosphate fluorophore moiety (PPi-fluorophore moiety), said phosphate fluoroscope moiety carries a second molecular charge (ie.,-3), wherein the difference between said first molecular charge (ie., -2 in the dNTP in Figure 4 wherein the fluorophore moiety do not bear any charge and the quencher moiety is cy3) and said second molecular charge (ie., -3 in PPi- fluorophore moiety) is at least 0.5 (ie., 1) as recited in claims 1 and 19. Since it is known that pyrophosphate (PPi) released from dNTP loses 0.26 unit of negative charge in pure water at pH 7 due to hydrogen ion equilibration with the terminal phosphate oxygen (see the specification, page 11, last paragraph and page 12, first paragraph), net charge of pyrophosphate (PPi)-the fluorophore moiety released from the dNTP in Figure 4 of Williams *et al.*, becomes -2.74 [-3 +(+0.26)=-2.74] at pH 7 instead of -3 under a ideal condition (without considering effects of a buffer). Therefore, the difference between said first molecular charge (ie., -2 in the dNTP in Figure 4 wherein the fluorophore moiety do not bear any charge and the quencher moiety is cy3) and said

second molecular charge (ie., -2.74 in ppi- fluorophore moiety) is at least 0.5 (ie., 0.74) as recited in claims 1 and 19. Since it is known that T7 DNA polymerase buffer contains Mg^{2+} (ie., 10 mM $MgCl_2$, see the attachment related to T7 DNA polymerase in previous office action) and Mg^{2+} binds to the terminal phosphate (ie. γ-phosphate) to neutralize negative charges of both dNTP and cleavage pyrophosphate (see the specification, second paragraph of page 12 and last paragraph of page 13), in the T7 DNA polymerase buffer, net charge of dNTP in Figure 4 of Williams *et al.*, and pyrophosphate (PPi)-the fluorophore moiety released from the dNTP in Figure 4 of Williams *et al.*, becomes 0 [-2+(+2)=0] and -1 [-3 +(+2)=-1] respectively. Therefore, the difference between said first molecular charge (ie., 0 in the dNTP in Figure 4 wherein the fluorophore moiety do not bear any charge and the quencher moiety is cy3) and said second molecular charge (ie., -1 in PPi- fluorophore moiety) in T4 polymerase buffer is at least 0.5 (ie., 1) as recited in claims 1 and 15-17. According to the definition, "terminal phosphate oxygen" is "the secondary ionization oxygen atom (PK ~6.5) attached to the terminal phosphate atom in a nucleotide phosphate probe." (see the specification, pages). Since Mg^{2+} in the T7 DNA polymerase buffer binds to the terminal phosphate (ie., γ-phosphate) and the secondary ionization oxygen atom attached to the terminal phosphate atom, a counter-cation (ie., Mg^{2+}) is indirectly associated with an ionized oxygen (ie., the secondary ionization oxygen atom is attached to the terminal phosphate atom) as recited in claims 15-17.

Regarding claims 2-4, 6-12, and 18, since the fluorophore is released from the dNTP in Figure 4 of Williams *et al.*, along with the pyrophosphate group after the cleavage, the intact NP probe (ie., dNTP in Figure 4 of Williams *et al.*,) is a nucleotide triphosphate wherein the PPi-fluorophore moiety is the terminal phosphate as recited in claim 3. Since the quencher moiety

of dNTP in Figure 4 is cy3 that carries a net single positive charge, the intact NP probe (ie., dNTP in Figure 4 of Williams *et al.,*) has a positive molecular charge as recited in claims 2 and 4. Since NTP probe taught by Williams *et al.,* can be dATP, dCTP, dGTP, dTTP, dUTP, ATP, CTP, GTP, and UTP (see columns 20 and 21, claims 15-17), claims 6-9 are anticipated by Williams *et al.*. Since fluorophore moiety is attached to γ phosphate of the dNTP via a linker wherein said linker is an alkylene group having between about 5 to about 12 carbons (see column 21, claims 20 and 21), claims 11 and 12 are anticipated by Williams *et al.*. Since various different fluorescence dyes such as BODIPY, FAM, and Texas Red (see column 12, line 44-67, and column 13, lines 1-19) are used as the fluorophore moiety of dNTP taught by Williams *et al.*, and it is known that Texas Red is also called as BODIPY TR, claims 10 and 18 are anticipated by Williams *et al.*.

Therefore, Williams *et al.,* teach all limitations recited in claims 1-4, 6-12, and 15-19.

Response to Arguments

In page 11, last paragraph bridging to page 13, first paragraph of applicant's remarks filed on February 24, 2004, applicant argues that: (1) in view of column 18, lines 10-17 of Williams, Figure 4 is DABCYL-succinimidyl ester conjugated to 5-allylamino dUTP; and (2) "[I]t is respectfully submitted that the Examiner is not permitted to 'assume that the dNTP in Figure 4, the fluorophore moiety does not bear any charge and the quencher is CY-3, ' without an express or inherent description of such a molecule. Applicants respectfully point out that the reference must anticipate the application without any additional assumption made by the Examiner".

These arguments have been fully considered but they are not persuasive toward the

withdrawal of the rejection. First, Figure 4 of Williams is not only limited to DABCYL-succinimidyl ester conjugated to 5-allylamino dUTP since B in Figure 4 can be one of adenine, guanine, cytosine, and uracil (see Figure 4). DABCYL-succinimidyl ester conjugated to 5-allylamino dUTP suggested by applicant is only one of compounds taught by Figure 4. Second, since various different fluorescence dyes such as cy3 or cy5 are used as the fluorophore moiety and the quencher moiety in fluorescence labeled dNTP (see columns 12 and 13), Williams must teach that, in one of dNTPs of Figure 4, its fluorophore moiety does not bear any charge and its quencher moiety is cy3. Thus the rejection is not based on the examiner's assumption but is based on the teachings of Williams.

5. Claims 1-4, 6-12, and 15-19 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The patent above teaches all limitations recited in claim 1-4, 6-12, and 15-19. However, there is only one inventor, John G. K. Williams in above patent. In contrast, the inventors of this application includes multiple inventors, John G.K. Williams, Jiyan Chen, Nara Narayanan, and Pamela Sheaff. Since inventors Gregory R. Bashford, Jiyan Chen, Dan Draney, Nara Narayanan, Bambi L. Reynolds, and Pamela Sheaff do not list in above patent and the patent above teaches all limitations recited in claim 1-4, 6-12, and 15-20, these people can not considered as inventors of this instant application.

Response to Arguments

In page 13, second to fourth paragraphs of applicant's remarks filed on February 24, 2004, applicant argues that "[I]n view of remarks set forth in section IV above, it is clear that

U.S. Patent No. 6,232,075 does not anticipate the present claims. Further, claims 1-19, 21 and claims 49-66 are pending in the present application, whereas the Examiner has rejected only claims 1-4, 6-12 and 15-20 under 35U.S.C. 102 § (f). In certain instances, the contribution of inventors other than John G.K.Williams, is embodied in claims other than rejected claims 1-4, 6-12 and 15-20. As such, Applicants respectfully request that the Examiner withdraw the rejection".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, as shown above ***Response to Arguments***, Patent No. 6,232,075 does anticipate the present claims. Second, since, as suggested by applicant, "the contribution of inventors other than John G.K.Williams, is embodied in claims other than rejected claims 1-4, 6-12 and 15-20", applicant is required to cancel or amend claims 1-4, 6-12 and 15-19 in order to overcome this rejection because Williams teaches all limitations recited in claims 1-4, 6-12, and 15-19.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-4, 6-12, 18, and 19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-28 of U.S. Patent No.6,232,075B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claims in this instant application is either anticipated by, or would have been obvious over, the reference claims. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Regarding claim 1-4, 6-12, and 19, claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 teach a nucleotide triphosphate (ie., dNTP) having a γ-phosphate with a fluorophore moiety attached thereto and a quencher moiety sufficiently proximal to said fluorophore moiety to prevent fluorescence of said fluorophore moiety wherein said quencher moiety is covalently bound to the base of said nucleotide triphosphate (ie., dNTP) and said quenched moiety is a rhodamine dye (see columns 20 and 21). Since a γ-phosphate of a nucleotide triphosphate (ie., dNTP) is attached to a fluorophore moiety and it is known that γ-phosphate of dNTP is a terminal phosphate, claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 teach an intact NP probe having a terminal phosphate with a fluoroscope moiety attached thereto as recited in claim 1 of this instant application. Since claim 18 of U.S. Patent No.6,232,075B1 shows that said fluorophore moiety can be a rhodamine dye and it is known that one of rhodamine dyes, rhodamine 110, with a net single positive charge (see attachment for rhodamine 110 in previous office), **in one of dNTPs recited in claims 12-15, 18, and 19 of U.S.**

Patent No.6,232,075B1 , its fluorophore moiety does not bear any charge and its quencher moiety is rhodamine 110. Since there is no pH in claim 1 of this instant application and claims 1-30 of U.S. Patent No.6,232,075B1, we consider that dNTP taught in claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 is in either a buffer with a pH 7 or a buffer with pH 7.5 because, as shown in U.S. Patent No.6,232,075B1, DABCYL-dUTP or DABCYL-dUTP-thiol or DABCYL-dUTP-BODIPY TR is stored in a buffer at pH 7 (ie.,Buffers A and B) after they are purified from a reversed-phase HPLC (see column 18, lines 61-67 and column 19, lines 1-29) and one of DNA polymerases used in U.S. Patent No.6,232,075B1 is T7 DNA polymerase (see column 6, lines 23-36 and column 18, lines 1-9) wherein pH for reaction buffer of T7 DNA polymerase is 7.5 (see above). Since dNTP recited in claims 12, 13, and 19 of U.S. Patent No.6,232,075B1 has three negative charges contributed by each ionizable oxygen atom on each phosphate of dNTP while the bases in dNTP are mostly uncharged at pH from about 6.5 to about 8.5 (see the specification, page 11, third paragraph), under an ideal condition (without considering effects of a buffer), net charge of the dNTP recited in claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 is -2. Since the fluorophore moiety can be released from the dNTP recited in claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 along with the pyrophosphate group after the cleavage wherein said fluorophore moiety does not bear any charge, under an ideal condition (without considering effects of a buffer), net charge of pyrophosphate (PPi)-the fluorophore moiety released from the dNTP recited in claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 is -3 (with three negative charges, for PPi structure, see Figure 1 of the specification). Therefore, under an ideal condition (without considering effects of a buffer), dNTP recited in claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 which has a γ

phosphate with a fluorophore moiety that does not bear any charge and has rhodamine 110 as a quencher moiety, is an intact NP probe having a terminal phosphate with a fluoroscope moiety attached thereto, said intact NP probe having a first molecular charge associated therewith (ie., -2), whereupon cleavage of said terminal phosphate as a phosphate fluorophore moiety (PPi-fluorophore moiety), said phosphate fluoroscope moiety carries a second molecular charge (ie., -3), wherein the difference between said first molecular charge (ie., -2 in the dNTP recited in claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1) and said second molecular charge (ie., -3 in PPi- fluorophore moiety) is at least 0.5 (ie., 1) as recited in claims 1 and 19 of this instant application. Since it is known that pyrophosphate (PPi) released from dNTP loses 0.26 unit of negative charge in pure water at pH 7 due to hydrogen ion equilibration with the terminal phosphate oxygen (see the specification, page 11, last paragraph and page 12, first paragraph), net charge of pyrophosphate (PPi)-the fluorophore moiety released from the dNTP of claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 becomes -2.74 [-3 +(+0.26)=-2.74] at pH 7.0 instead of -3 under a ideal condition (without considering effects of a buffer). Therefore, the difference between said first molecular charge (ie., -2 in the dNTP recited in claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 wherein the fluorophore moiety does not bear any charge and the quencher moiety is rhodamine 110) and said second molecular charge (ie., -2.74 in PPi-fluorophore moiety) in pure water pH 7 is at least 0.5 (ie., 0.74) as recited in claim 20. Since the fluorophore is released from the dNTP of claims 12-15, 18, and 19 of U.S. Patent No. 6,232,075B1 along with the pyrophosphate group after the cleavage, the dNTP taught by claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 is a nucleotide triphosphate wherein the PPi-fluorophore moiety is the terminal phosphate as recited in claim 3. Since the quencher moiety

of dNTP of claims 12-15, 18, and 19 of U.S. Patent No.6,232,075B1 is rhodamine 110 that carries a net single positive charge, dNTP taught in claims 12-15, 18, and 19 of U.S. Patent No. 6,232,075B1 has a positive molecular charge as recited in claims 2 and 4. Note that claims 6-12 of this instant application are identical to claims 14-17 and 19-21 of U.S. Patent No.6,232,075B1.

Regarding claim 18, since claims 19 and 27 of U.S. Patent No.6,232,075B1 teach that said fluorophore moiety is BODIPY dyes and it is known that BODIPY TR is one kind of BODIPY dyes, claims 19 and 27 of U.S. Patent No.6,232,075B1 teach claim 18 of this instant application.

Therefore, although claims 1-4, 6-12, 18, and 19 in this instant application are not identical to claims 12-28 of U.S. Patent No.6,232,075B1, claims 12-28 of U.S. Patent No.6,232,075B1 are directed to the same subject matter and fall entirely within the scope of claims 1-4, 6-12, 18, and 19 in this instant application. In other words, claims 1-4, 6-12, 18, and 19 in this instant application are anticipated by claims 12-28 of U.S. Patent No.6,232,075B1.

Response to Arguments

In page 1 of applicant' remarks filed on May 27, 2004, applicant indicates that "Applicants respectfully request that the examiner hold this rejection in abeyance until all the subject matter of the matter invention is in condition for allowance. At that time, Applicants will take the necessary steps to obviate double patenting rejection by filling a Terminal Disclaimer".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection because applicant does not file a terminal disclaimer in response to the office action mailed on October 20, 2003.

Assignee Required

8. As shown above, claims 1-4, 6-12, 18, and 19 are directed to an invention not patentably distinct from claims 12-28 of commonly assigned U.S. Patent No.6,232,075B1 (for detail, see above). The Examiner notes that this instant applicant was filed on June 6, 2001. However, an assignment of this instant application was recorded by the office on October 9, 2001, which was four months later than filing date of this instant application. Note that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned US application 09/876,374 (this instant application) and U.S. Patent No.6,232,075B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C.102(e) for applications filed on or after November 29, 1999.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Note that claims 4 and 5 that were objected in previous office action now are rejected under 35 U.S.C 102 since applicant has changed dependency of claims 4 and 5 in the amendment filed on February 24, 2004.

11. Claims 13, 14, 21, 52, and 54-66 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of

such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
September 23, 2004

BJ FORMAN, PH.D.
PRIMARY EXAMINER